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CLINICAL PRACTICE GUIDELINES

Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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Incidence and epidemiology

Multiple myeloma (MM) accounts for 1% of all cancers and ∼10% of all haematological malignancies. The incidence in Europe is 4.5–6.0/100 000/year with a median age at diagnosis of 72 years; the mortality is 4.1/100 000/year [1]. Almost all patients with MM evolve from an asymptomatic pre-malignant stage termed monoclonal gammopathy of undetermined significance (MGUS). MGUS progresses to MM at a rate of 1% per year. In some patients, an intermediate asymptomatic but more advanced pre-malignant stage termed smouldering (or indolent) MM (SMM) can be recognised. SMM progresses to myeloma at a rate of 10% per year over the first 5 years following diagnosis, 3% per year over the following 5 years, and 1.5% per year thereafter [2].

Diagnosis and pathology/molecular biology

Diagnosis of MM should be based on the following tests [3, 4]:

- Detection and evaluation of the monoclonal (M) component by serum and/or urine protein electrophoresis (concentrate of 24h urine collection); nephelometric quantification of IgG, IgA and IgM immunoglobulins; characterisation of the heavy and light chains by immunofixation; and serum-free light-chain (FLC) measurement.
- Evaluation of bone marrow (BM) plasma cell infiltration: BM aspiration and/or biopsies are the standard options to evaluate the number and characteristics of plasma cells in BM. Moreover, the BM sample should be used for cytogenetic/flurorescent *in situ* hybridisation (FISH) studies on immunologically recognised or sorted plasma cells and also has the potential for immunophenotypic and molecular investigations.
- Evaluation of lytic bone lesions: whole-body low-dose computed tomography (WBLD-CT) is the new standard for the diagnosis of lytic disease. Conventional radiography can also be used if WBLD-CT is not available. Magnetic resonance imaging (MRI) provides greater details and is recommended whenever spinal cord compression is suspected. Either whole-body MRI or MRI of the spine and the pelvis may be used, according to their availability, to assess the BM plasma cell infiltration, in particular the presence of bone focal lesions. 18F-fluorodeoxyglucose positron emission tomography with CT (PET-CT) can be done to evaluate bone lesions, according to availability and resources.
- Complete blood cell count, with differential serum creatinine, creatinine clearance and calcium level.

These tests can allow for the differential diagnosis between MM, SMM and MGUS.

The criteria for diagnosis of MM were updated in 2014 by the International Myeloma Working Group (IMWG) [2]. The

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diagnosis requires ≥10% clonal BM plasma cells or biopsy-proven bony or extra-medullary plasmacytoma and any of the following myeloma-defining events (Table 1):

- Evidence of end-organ damage (the so-called CRAB criteria: hypercalcaemia, renal insufficiency, anaemia or bone lesions) that is felt to be related to the underlying plasma cell disorder. Of note, renal insufficiency can be defined not only by creatinine > 2 mg/dL but also by creatinine clearance < 40 mL/min [measured by validated equations such as the Modification of Diet in Renal Disease (MDRD) or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)] [4]. Moreover, lytic lesions can also be defined by CT and not only by conventional X-ray.
- Any biomarkers of malignancy:
  - ≥ 60% clonal BM plasma cells
  - Involved/uninvolved serum FLC ratio ≥ 100
  - > 1 focal lesion on MRI studies (each focal lesion must be ≥ 5 mm in size).

Staging and risk assessment

The course of MM is highly variable, and the clinical behaviour is remarkably heterogeneous. Many studies have identified prognostic factors capable of predicting this heterogeneity in survival: serum β2-microglobulin, albumin, C-reactive protein and lactate dehydrogenase (LDH).

The International Staging System (ISS), a powerful and reproducible three-stage classification (Table 2), relies on the combination of serum levels of β2-microglobulin and albumin. ISS stage III is associated with the poorest outcome [5].

Cytogenetics, evaluated by FISH, is a major prognostic factor. Three recurrent genetic abnormalities, t(4;14), deletion(17p) and t(14;16), are mostly associated with a poorer outcome. Chromosome 1 abnormalities are also adverse prognostic factors [6].

It has recently been demonstrated that combining FISH and LDH, along with the ISS stage, could significantly improve the prognostic assessment in terms of progression-free survival (PFS) and overall survival (OS), according to this new and revised ISS (R-ISS) (Table 3) [7]. Median PFS was 66 months for patients with R-ISS stage I, 42 months for patients with R-ISS stage II and 29 months for patients with R-ISS stage III. The 5-year OS was 82% for R-ISS stage I, 62% for R-ISS stage II and 40% for R-ISS stage III. Median OS time was not reached for patients with R-ISS stage I and was of 83 and 43 months for R-ISS stage II and R-ISS stage III patients, respectively [7].

Gene-expression profiling may segregate patients with standard or high-risk disease, but this test is not yet established in routine practice.

Elderly patients with myeloma are heterogeneous and assessment strategies should be considered before starting therapy to define the frailty profile of the patient. The IMWG has proposed

Table 2. International staging system for MM

Stage	Criteria
I	Serum β2M < 3.5 mg/mL and serum albumin ≥ 3.5 g/dL
II	Not stage I or III[a]
III	Serum β2M ≥ 5.5 mg//mL

[a]There are two possibilities for stage II:
- Serum β2M < 3.5 mg/L but serum albumin < 3.5 g/dL;

or
- Serum β2M 3.5–5.5 mg/L irrespective of the serum albumin.

β2M, β2 microglobulin; MM, multiple myeloma.
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Table 1. Diagnostic criteria for plasma cell disorders

Plasma cell disorder	Definition
Smouldering multiple myeloma	Both criteria must be met: • Serum M protein (IgG or IgA) ≥ 30 g/L or urinary M protein ≥ 500 mg per 24 h and/or clonal BM plasma cells 10%–60% • Absence of myeloma-defining events or amyloidosis
Multiple myeloma	Clonal BM plasma cells ≥ 10% or biopsy-proven bony or extramedullary plasmacytoma and any one or more of the following myeloma-defining events: • Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically: - Hypercalcaemia: serum calcium > 0.25 mmol/L (> 1 mg/dL) higher than the upper limit of normal or > 2.75 mmol/L (> 11 mg/dL) - Renal insufficiency: CrCl < 40 mL/min or serum creatinine > 177 μmol/L (> 2 mg/dL) - Anaemia: haemoglobin value of > 20 g/L below the lower limit of normal or a haemoglobin value < 100 g/L - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT or PET-CT • Any one or more of the following biomarkers of malignancy: - ≥ 60% clonal BM plasma cells - Involved/uninvolved serum-free light chain ratio ≥ 100 - > 1 focal lesion on MRI studies (each focal lesion must be ≥ 5 mm in size)

BM, bone marrow; CrCl, creatinine clearance; CT, computed tomography; M protein, monoclonal protein; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography.
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Table 3. Standard risk factors for MM and the revised ISS

Prognostic factor	Criteria
ISS stage	
I	Serum β2M < 3.5 mg/L, serum albumin ≥ 3.5 g/dL
II	Not ISS stage I or III
III	Serum β2M ≥ 5.5 mg/L
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH < the upper limit of normal
High	Serum LDH > the upper limit of normal
A new model for risk stratification for MM	
R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH

β2M, β2 microglobulin; CA, chromosomal abnormalities; iFISH, interphase fluorescent *in situ* hybridisation; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; R-ISS, revised International Staging System.

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a frailty score (an additive scoring system based on age, comorbidities and cognitive and physical conditions) that predicts mortality and the risk of toxicity in this group of patients [8].

Response evaluation

The definition of response established by the IMWG in 2006 has been updated twice, in 2011 [9] and in 2016 [10] (Tables 4 and 5). The quality and the depth of response have improved over the last 5 years in the context of novel agent-based therapies, allowing for the introduction of new response grades, namely minimal residual disease (MRD) criteria including sequencing MRD negativity, flow MRD negativity, imaging plus negativity and sustained MRD negativity. Nevertheless, MRD evaluation is not yet a reimbursed procedure, does not lead to treatment decisions, and is currently being evaluated in the context of clinical trials.

There is a statistical relationship between the achievement of complete response (CR), MRD negativity and PFS or OS.

Front-line treatment

Smouldering myeloma

Immediate treatment is not recommended at the present time for patients with indolent myeloma. Clinical trials for high-risk smouldering myeloma are strongly encouraged.

Multiple myeloma

Treatment should be initiated in all patients with MM according to the updated definition proposed by the IMWG in 2014 [2]. Major treatment regimens in MM are shown in Table 6. Front-line treatment regimens are shown in Figure 1.

Elderly patients (non-transplant setting). The two following options are recommended based on data from randomised phase III trials [I, A]: bortezomib (administered subcutaneously)/melphalan/prednisone (VMP) [11] or lenalidomide plus low-dose dexamethasone (Rd) [12]; both VMP and Rd are approved in this setting by the European Medicines Agency (EMA). Rd is approved until progression of the disease. Melphalan/prednisone/thalidomide (MPT) [13] is also approved by the EMA, but is inferior to Rd in terms of PFS and OS [12]. Bortezomib-cyclophosphamide and dexamethasone (VCD) is not EMA-approved (no controlled data), but is widely used and induces high response rates and prolonged PFS [III, A] [14]. Rd has recently been compared prospectively with Rd plus bortezomib (VRd), and the addition of bortezomib resulted in significantly improved PFS and OS and had an acceptable risk–benefit profile [15]. Nevertheless, this triplet combination is not yet approved by the EMA. Bendamustine plus prednisone is also approved by the EMA in patients who have clinical neuropathy at time of diagnosis, precluding the use of thalidomide according to the MPT regimen or bortezomib according to the VMP regimen [II, C] [16].

Melphalan/prednisone/lenalidomide (MPR) has been evaluated in two prospective randomised studies versus melphalan and prednisone (MP) [17] and versus MPT [18], but MPR was not superior to the other combinations with a fixed number of cycles [II, C]. This triplet combination is approved by the EMA but is not routinely used and cannot be considered as a standard of care.

Cyclophosphamide/thalidomide/dexamethasone (CTD) has also been compared with MP and is superior in terms of response rates, but does not induce a clear survival advantage over MP [II, C] [19].

Younger patients (< 65 years or fit patients < 70 years in good clinical condition). For patients in good clinical condition (e.g. fit patients), induction followed by high-dose therapy (HDT) with autologous stem cell transplantation (ASCT) is the standard treatment [II, B] [14]. Two recent phase III trials comparing front-line ASCT versus ASCT at the time of first relapse showed that PFS was improved in the front-line ASCT arm (in the context of triplet novel agent-based induction) [20, 21]. Response rates to induction therapy have been significantly increased by the use of novel agent-based combinations. Bortezomib-dexamethasone, which is superior to the classical VAD regimen (vincristine, doxorubicin and high-dose dexamethasone) [II, B], has become the backbone of induction therapy before ASCT [14]. The addition of a third agent to bortezomib-dexamethasone, e.g. thalidomide (VTD), doxorubicin (PAD), lenalidomide (RVD) or cyclophosphamide (VCD), has shown higher response rates in phase II trials [14]. Three prospective studies have already shown that VTD is superior to thalidomide-dexamethasone (TD) or bortezomib-dexamethasone [I, A] [14].

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Table 4. 2011 response criteria

Response subcategory	Response criteria
Molecular CR	CR plus negative ASO-PCR, sensitivity 10^{-5}
Immunophenotypic CR	Stringent CR plus Absence of phenotypically aberrant PCs (clonal) in BM with a minimum of 1 million total BM cells analysed by multiparametric flow cytometry (with > 4 colours)
Stringent CR	CR as defined below plus Normal FLC ratio and Absence of clonal PCs by immunohistochemistry or 2- to 4-colour flow cytometry
CR	Negative immunofixation on the serum and urine and Disappearance of any soft tissue plasmacytomas and ≤ 5% PCs in BM
VGPR	Serum and urine M protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M protein plus urine M protein level <100 mg per 24 h
PR	≥ 50% reduction of serum M protein and reduction in 24h urinary M protein by ≥ 90% or to < 200 mg per 24 h If the serum and urine M protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M protein criteria If serum and urine M protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥ 50% reduction in PCs is required in place of M protein, provided baseline BM PC percentage was ≥ 30% In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
Progressive disease	Increase of 25% from lowest confirmed response value in one of the following criteria: Serum M protein (absolute increase must be ≥ 0.5 g/dL) Serum M protein increase ≥ 1 g/dL, if the lowest M component was ≥ 5 g/dL Urine M protein (absolute increase must be ≥ 200 mg/24 h)

ASO-PCR, allele-specific polymerase chain reaction; BM, bone marrow; CR, complete response; FLC, free light chain; M protein, monoclonal protein; PCs, plasma cells; PR, partial response; VGPR, very good partial response.
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Table 5. 2016 response criteria

Response subcategory		Response criteria
IMWG MRD negativity criteria	Sustained MRD-negative	MRD-negative in the marrow (next-generation flow and/or NGS) and by imaging as defined below, confirmed one year apart. Subsequent evaluations can be used to further specify the duration of negativity (e.g. MRD-negative at 5 years)
	Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by next-generation flow cytometry on BM aspirates using the EuroFlow standard operation procedure for MRD detection in MM (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
	Sequencing MRD-negative	Absence of clonal plasma cells by NGS on BM aspirates in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of BM aspirates using the Lymphosight® platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
	Imaging + MRD-negative	MRD-negative as defined by next-generation flow cytometry or NGS plus Disappearance of every area of increased tracer uptake found at baseline or a preceding PET-CT or decrease to < mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue

BM, bone marrow; IMWG, International Myeloma Working Group; MM, multiple myeloma; MRD, minimal residual disease; NGS, next-generation sequencing; PET-CT, positron emission tomography-computed tomography; SUV, standardised uptake value.
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Table 6. Major treatment regimens in multiple myeloma

Regimen	Usual dosing schedule
Front-line:	
Bortezomib/melphalan/prednisone (VMP) [11]	Bortezomib 1.3 mg/m^2 subcutaneously days 1, 8, 15, 22; melphalan 9 mg/m^2 orally days 1–4; prednisone 60 mg/m^2 orally days 1–4; repeated every 35 days
Lenalidomide/low-dose dexamethasone (Rd) [12]	Lenalidomide 25 mg orally days 1–21; dexamethasone 40 mg orally days 1, 8, 15, 22; repeated every 28 days
Melphalan/prednisone/thalidomide (MPT) [13]	Melphalan 0.25 mg/kg orally days 1–4 (use 0.20 mg/kg/day orally days 1–4 in patients over the age of 75); prednisone 2 mg/kg orally days 1–4; thalidomide 100–200 mg orally days 1–28 (use 100 mg dose in patients >75); repeated every 6 weeks
Bortezomib/cyclophosphamide/dexamethasone (VCD) [14]	Cyclophosphamide 300 mg/m^2 orally days 1, 8, 15 and 22; bortezomib 1.3 mg/m^2 i.v. on days 1, 8, 15, 22; dexamethasone 40 mg orally on days 1, 8, 15, 22; repeated every 4 weeks
Bortezomib/thalidomide/dexamethasone (VTD) [14]	Bortezomib 1.3 mg/m^2 subcutaneously days 1, 8, 15, 22; thalidomide 100–200 mg orally days 1–21; dexamethasone 20 mg on day of and day after bortezomib (or 40 mg days 1, 8, 15, 22); repeated every 4 weeks × 4 cycles as pre-transplant induction therapy
Bortezomib/lenalidomide/dexamethasone (VRd) [14]	Bortezomib 1.3 mg/m^2 subcutaneously days 1, 8, 15; lenalidomide 25 mg orally days 1–14; dexamethasone 20 mg on day of and day after bortezomib (or 40 mg days 1, 8, 15, 22); repeated every 3 weeks
Relapse/refractory disease:	
Carfilzomib/lenalidomide/dexamethasone (KRd) [24, 32]	Carfilzomib 20 mg/m^2 (cycle 1) and 27 mg/m^2 (subsequent cycles) i.v. on days 1, 2, 8, 9, 15, 16; lenalidomide 25 mg orally days 1–21; dexamethasone 40 mg on days 1, 8, 15, 22; 28-day cycles
Bortezomib/dexamethasone/panobinostat (VD-Pano) [31]	Bortezomib 1.3 mg/m^2 subcutaneously days 1, 8, 15, 22; dexamethasone 20 mg on day of and day after bortezomib; panobinostat 20 mg orally days 1, 3, 5 week 1 and 2; repeated every 3 weeks (cycles 1–8)
Carfilzomib/dexamethasone (Kd) [33]	Carfilzomib 56 mg/m^2 i.v. days 1, 2, 8, 9, 15, 16 (20 mg/m^2 days 1, 2, cycle 1 only); dexamethasone 20 mg days 1, 2, 8, 9, 15, 16, 22, 23; 28-day cycles
Lenalidomide/dexamethasone/elotuzumab (Rd-Elo) [34]	Lenalidomide 25 mg orally days 1–21; dexamethasone 40 mg weekly; elotuzumab 10 mg/kg i.v. weekly cycle 1 and 2, every other week cycles 3+; repeated every 28 days
Lenalidomide/dexamethasone/ixazomib (IRd) [35]	Lenalidomide 25 mg orally days 1–21; dexamethasone orally 40 mg days 1, 8, 15, 22; ixazomib 4 mg orally days 1, 8, 15; repeated every 28 days
Bortezomib/dexamethasone/daratumumab (DVd) [38]	Bortezomib 1.3 mg/m^2 subcutaneously days 1, 4, 8, 11 (cycles 1–8); dexamethasone 20 mg orally days 1, 2, 4, 5, 8, 9, 11, 12 (cycles 1–8); daratumumab 16 mg/kg i.v. every week (cycles 1–3), every 3 weeks (cycles 4–8), every 4 weeks (cycles 9+); cycles 1–8: repeated every 21 days; cycles 9+: repeated every 28 days
Lenalidomide/dexamethasone/daratumumab (DRd) [39]	Lenalidomide 25 mg orally days 1–21; dexamethasone 40 mg orally weekly; daratumumab 16 mg/kg i.v. weekly (cycles 1-2), every other week (cycles 3-6), every 4 weeks (cycles 7+)

Two trials have prospectively compared VCD versus PAD [II, B] [22], and VTD versus VCD [II, B] [23]. The first one showed that VCD and PAD were equally effective in terms of response, and that VCD was less toxic. The second one showed that VTD is the more effective regimen compared with VCD in terms of very good partial response rates, but was associated with a higher rate of peripheral neuropathy. Based on response rates, depth of response and PFS as surrogate markers for outcome, three-drug combinations including at least bortezomib and dexamethasone are currently the standard of care before ASCT [14]. In Europe, VTD and VCD are the most preferred regimens [14]. RVD, when approved, will probably be widely used [20]. Carfilzomib-lenalidomide and dexamethasone (KRd) [24], currently being evaluated in ongoing phase III trials, is associated with high response rates, but is currently only approved for treatment of relapsed MM.

Four to six courses of induction are recommended before proceeding to stem cell collection.

Melphalan [200 mg/m^2 intravenous (i.v.)] is the standard preparative regimen before ASCT [II, B] [25]. Peripheral blood progenitor cells are the preferred source of stem cells, rather than BM [III, B] [14].

Tandem ASCT was evaluated before the era of novel agents. The benefit of tandem ASCT was observed in patients not achieving very good partial response after the first ASCT [14]. In a recent study from The Netherlands and Germany (HOVON-65/GMMG-HD4 trial), in the context of bortezomib induction and maintenance treatment, OS was better in the GMMG group (tandem ASCT) in contrast to the HOVON group (single ASCT) [26]. Nevertheless, the trial was not powered to compare single versus double ASCT. The recent EMN02/H095 trial compared single versus tandem ASCT upfront; PFS was improved in the tandem ASCT arm of the study, hampered by a short follow-up [21]. Additional data from a similar trial (BMT CTN 0702, NCT01109004) being conducted in the USA will solve this important issue.

Allogeneic SCT is not indicated as part of front-line therapy and should only be carried out in the context of a clinical trial.

Consolidation

Several trials have shown that consolidation is improving the depth of response [14]. However, in the era of novel agent-based

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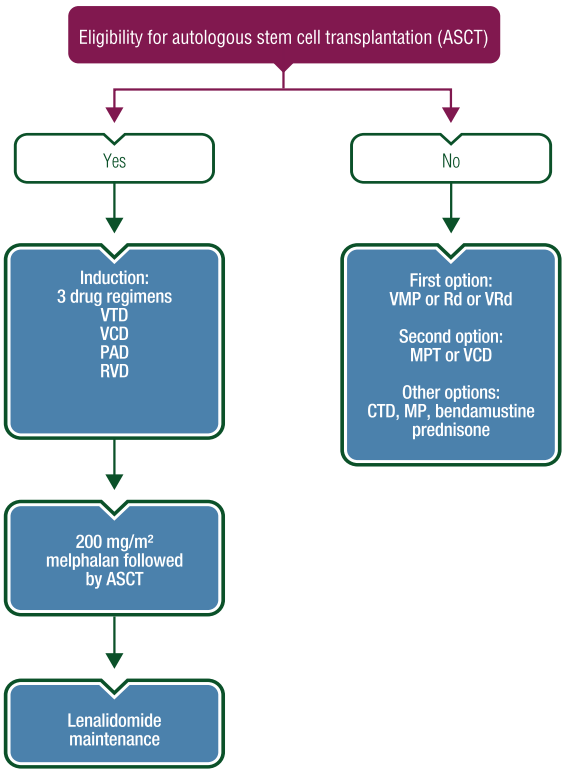

Figure 1. Front-line treatment of symptomatic multiple myeloma outside clinical trials.
CTD, cyclophosphamide, thalidomide, dexamethasone; MP, melphalan, prednisone; MPT, melphalan, prednisone, thalidomide; PAD, bortezomib, doxorubicin, dexamethasone; Rd, lenalidomide, low-dose dexamethasone; RVD, lenalidomide, bortezomib, dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; VMP, bortezomib, melphalan, prednisone; VRd, lenalidomide, low-dose dexamethasone, bortezomib; VTD, bortezomib, thalidomide, dexamethasone.

induction therapy, there is still not enough evidence that consolidation therapy should be systematically applied. Ongoing trials will clarify the impact of consolidation, especially in the setting of front-line ASCT, such as the EMN02/H095 and BMT CTN 0702 studies.

Maintenance

In elderly patients following induction, several randomised trials have explored the benefit of maintenance therapy in terms of OS using either immunomodulatory drugs (IMiDs) or bortezomib: MP or a reduced-dose regimen of CTD (CTDa) with or without thalidomide maintenance [19], MP versus MPR versus MPR-R [17], VMPT-VT versus VMP [27], VMP versus VTP followed by either VP or VT maintenance [28]. These trials have not demonstrated a clear benefit in OS, and the drugs are not yet approved by the EMA; therefore, systematic maintenance therapy currently cannot be recommended in elderly patients.

In young patients following ASCT, phase III randomised trials have demonstrated that maintenance therapy with IMiDs, either thalidomide or lenalidomide, prolongs PFS [I, A] [14]. A recent meta-analysis based on individual patient data of more than 1200 cases demonstrated that lenalidomide maintenance following ASCT is associated with an overall OS benefit of more than two years [I, A] [29]. In February 2017, the EMA approved lenalidomide as monotherapy for the maintenance treatment of adult patients with newly diagnosed MM who have undergone ASCT. Bortezomib maintenance was also evaluated during a two-year study and was associated with a survival benefit over thalidomide maintenance, but induction was not identical in the two arms of this prospective trial [26]. Bortezomib and thalidomide are not approved in this setting.

Treatment of relapsed/refractory disease

The choice of therapy in the relapse setting depends on several parameters such as age, performance status, comorbidities, the type, efficacy and tolerance of the previous treatment, the number of prior treatment lines, the available remaining treatment options, the interval since the last therapy and the type of relapse (i.e. clinical versus biochemical relapse; in the case of biochemical relapse, treatment can be delayed) (Table 6) [30].

Until 2015, the EMA had approved, at the time of first relapse and beyond, lenalidomide in combination with dexamethasone [I, A] and bortezomib, either alone as single-agent or in combination with PEGylated doxorubicin [I, A]. Nevertheless, bortezomib is mostly used in combination with dexamethasone in the relapse setting [30].

In 2015 and 2016, based on the results of phase III prospective randomised trials, new triplet combinations were approved by the EMA. Panobinostat, a panHDAC inhibitor, in combination with bortezomib and dexamethasone, is now indicated for the treatment of patients with relapsed/refractory MM who have received at least two prior regimens including bortezomib and an immunomodulatory agent [II, C] [31]. Carfilzomib, the second-in-class proteasome inhibitor, has also been approved at the dose of 27 mg/m^2 in combination with lenalidomide and dexamethasone for the treatment of patients with MM who have received at least one prior therapy [II, A] [32]. Carfilzomib has also been approved at the dose of 56 mg/m^2 in combination with dexamethasone alone in patients with at least one line of prior therapy [II, A] [33]. Elotuzumab, a monoclonal antibody targeting SLAM-F7, has also been approved in combination with lenalidomide and dexamethasone for the treatment of MM in patients who have received at least one prior therapy [II, B] [34]. Ixazomib, the first oral proteasome inhibitor, in combination with lenalidomide and dexamethasone was also approved by the EMA in 2016 in patients who have received at least one prior line of therapy [II, A] [35].

In very advanced-stage disease, two other drugs are EMA-approved for the treatment of relapsed MM. Pomalidomide, the third-in-class IMiD, in combination with low-dose dexamethasone, is approved in patients who have received at least two prior therapies, including both lenalidomide and bortezomib, and whose disease progressed after treatment with these medicines [II, A] [36]. Daratumumab, a monoclonal antibody targeting CD38, was also recently approved for the treatment of adults with relapsed/refractory MM whose previous treatment included a proteasome inhibitor and an immunomodulatory agent and whose

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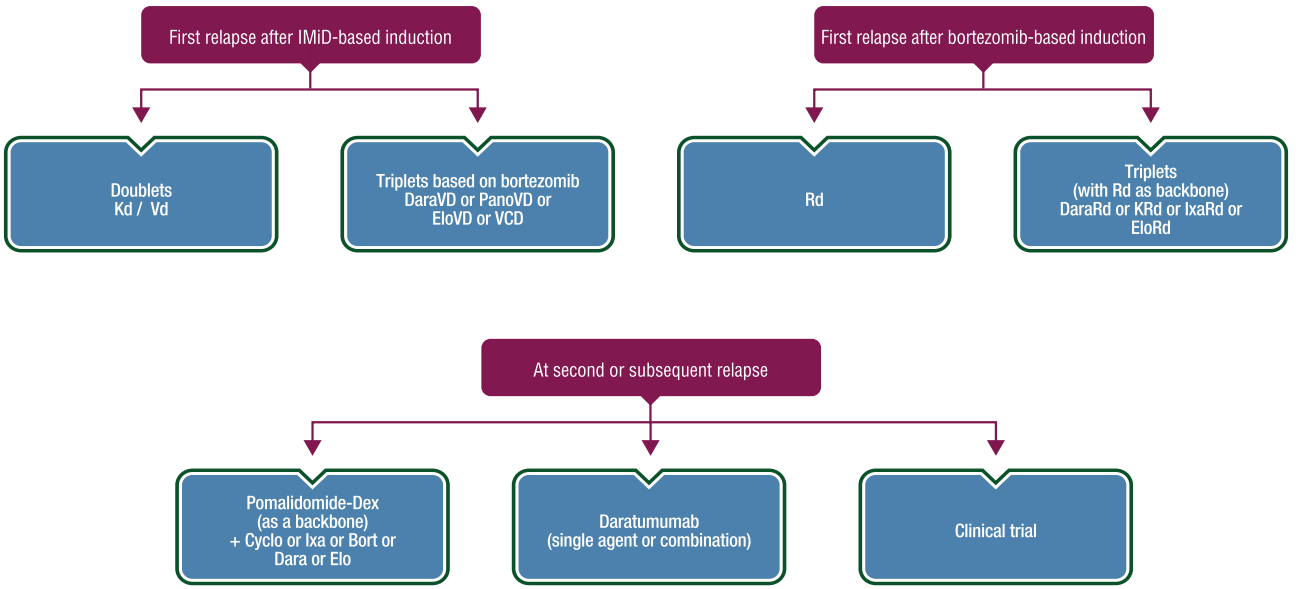

Figure 2. Treatment of relapse.
Bort, bortezomib; Cyclo, cyclophosphamide; Dara, daratumumab; DaraRd, daratumumab, lenalidomide, low dose dexamethasone; DaraVD, daratumumab, bortezomib, dexamethasone; Dex, dexamethasone; Elo, elotuzumab; EloRd, elotuzumab, lenalidomide, low dose dexamethasone; EloVD, elotuzumab, bortezomib, dexamethasone; IMiD, immunomodulatory drug; Ixa, izaxomib; IxaRd, izaxomib, lenalidomide, low dose dexamethasone; Kd, carfilzomib, low dose dexamethasone; KRd, carfilzomib, lenalidomide, low dose dexamethasone; PanoVD, panobinostat, bortezomib, dexamethasone; Rd, lenalidomide, low-dose dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; Vd, bortezomib, low dose dexamethasone.

disease worsened after treatment [II, A] [37]. Daratumumab has also shown significant efficacy at earlier stages of the disease, first relapse and beyond in combination with bortezomib-dexamethasone [II, A] [38] or lenalidomide-dexamethasone [II, A] [39] in two randomised phase III clinical trials. These two new triplet combinations may be considered in the near future as standards of care, in the case of regulatory approval.

In young patients, a second ASCT may be considered, provided that the patient responded well to the previous ASCT and had a PFS of more than 24 months [40]. In the relapse setting, allogeneic SCT should only be carried out in the context of a clinical trial.

When possible, patients should be offered participation in clinical trials.

Treatment of relapse is shown in Figure 2.

Management of solitary plasmacytoma

The diagnostic criteria require the existence of a histologically-confirmed solitary plasma cell tumour in the absence of BM infiltration and CRAB symptoms [41]. Local radiotherapy is the preferred treatment of choice, but about two-thirds of patients develop MM at 10 years' follow-up [42]. Moreover, following the use of high sensitivity flow cytometry, half of the patients showed occult BM infiltration, and half of these cases progressed at 2 years [43].

Management of plasma cell leukaemia

The outcomes of patients with plasma cell leukaemia (PCL) remains uniformly poor, with a median OS of only around 1 year [44]. There are no specific treatment approaches for PCL. The use of multidrug combinations (including both a proteasome inhibitor and an IMiD) appears to be a logical choice, along with the use of HDT in eligible patients, followed by prolonged maintenance until progression [44]. The role of novel agents such as monoclonal antibodies and immunotherapies, as well as metronomic approaches and allogeneic transplant should be formally investigated in these patients.

Supportive care

Bone disease and spinal cord compression

The i.v. agents pamidronate and zoledronic acid are of clinical benefit in the treatment of bone disease in patients with MM [II, A] [4]. Pamidronate is administered at a monthly dose of 90 mg via a 2 h i.v. infusion. Zoledronic acid is at least as effective as pamidronate at a monthly dose of 4 mg and has the advantage to be administered via a 15 min infusion. In patients with moderate renal function impairment (creatinine clearance 30–60 mL/min), the dose of zoledronic acid must be reduced to a maximum of 3 mg with no change to infusion time, while pamidronate should be given via a 4 h infusion [4]. Patients with hypercalcaemia should also receive zoledronic acid. The most challenging complication is osteonecrosis of the jaw. The current recommendations based on consensus panels from both the IMWG and the American Society of Clinical Oncology do not recommend the initial use of bisphosphonates for more than 2 years [4, 45]. In relapsed patients, treatment with bisphosphonates can be restarted and administered concomitantly with active therapy. New molecules such as denosumab are under investigation. Orthopaedic surgery is required in patients with pathological fractures or at risk of long bones, and may need to be complemented with radiotherapy [4, 45]. Patients with severe back pain due to vertebral compression fractures can benefit from vertebroplasty or kyphoplasty [4, 45].

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Spinal cord compression is an emergency that requires treatment with high-dose dexamethasone and simultaneous local radiotherapy should be started as soon as possible; surgery should be used in the case of bone fragments within the spinal route [4].

Anaemia, BM failure and infections

Recombinant human erythropoietin and darbepoetin alfa can be used for the treatment of myeloma-associated anaemia (haemoglobin level < 10 g/dL), once other causes of anaemia have been excluded [4]. The target is to maintain haemoglobin around 12 g/dL (below 14 g/dL to avoid thromboembolic complications and hypertension) [II, B] [46].

Treatment with granulocyte colony-stimulating factor (G-CSF) may be required to treat chemotherapy-induced severe granulocytopaenia. Infectious episodes require immediate therapy with broad spectrum antibiotics. Prophylaxis of infection remains controversial but may be beneficial within the first 2–3 months of initiation of therapy, especially in patients receiving lenalidomide or pomalidomide, or in patients at high risk of infection (previous serious infections or neutropaenia) [4]. Influenza and pneumococcal vaccinations are recommended [4]. Acyclovir or valacyclovir for herpes-zoster virus prophylaxis is recommended for patients receiving proteasome inhibitor-based therapies [4]. i.v. immunoglobulin prophylaxis is not routinely recommended [4].

Renal failure

Bortezomib-based therapies (in combination with dexamethasone ± thalidomide or doxorubicin or cyclophosphamide) is the treatment of choice in patients with renal failure [II, B] [4, 47]. Other proteasome inhibitors are under investigation. The use of high cut-off dialysis filters to remove FLCs or to reverse renal failure is under evaluation in randomised trials.

Venous thromboembolism. Patients with MM have an increased risk of thrombosis, with a baseline risk of 3%–4% of venous thrombotic events, and this risk is significantly enhanced in the face of therapy with use of specific agents. High-dose dexamethasone, cytotoxic chemotherapy such as doxorubicin and IMiDs (thalidomide and lenalidomide) increase this risk substantially. Other factors such as reduced mobility due to neurological complications or bone pain, associated fractures, concurrent use of erythropoiesis-stimulating agents and prior personal or family history of thrombotic events increase the risk of thromboembolic events. The current recommendations for patients with MM who are due to start IMiD therapy are to use aspirin (100 mg) in the absence of risk factors for thrombosis and to use full dose anticoagulants for those at higher risk (low molecular weight heparin or full-dose warfarin) [4]. Sub-therapeutic doses of anticoagulants such as small doses of warfarin are not recommended.

Personalised medicine

In 2016, no prognostic factor or staging system, including R-ISS or gene-expression profiling, is used routinely to define a risk-adapted strategy. In this disease setting, more research is needed to identify molecular markers which could lead to advances in personalised medicine.

Follow-up, long-term implications and survivorship

Full blood count, serum and urine electrophoresis and/or serum-FLC determination, creatinine and calcium should be carried out every 2–3 months (outside the context of a clinical trial). Serum-FLC may contribute to detect light chain escape.

In the case of bone pain, skeletal X-ray, MRI, WBLD-CT or PET-CT should be carried out to detect new bone lesions.

MM has for a long time been considered as an incurable disease. Recent trials incorporating novel agents and ASCT identify CR as an important predictor of long-term survival for transplant eligible MM patients, with a statistical cure fraction of ∼15% [48]. These numbers will increase with the addition of quadruplet combinations including monoclonal antibodies as part of front-line therapies.

Methodology

These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology. The relevant literature has been selected by the expert authors. A summary of recommendations is shown in Table 7. Levels of evidence and grades of recommendation have been applied using the system shown in Table 8. Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty. This manuscript has been subjected to an anonymous peer review process.

Disclosure

PM has reported advisory boards and honoraria from Celgene, Janssen, Takeda, Amgen and Novartis; JSM has reported advisory boards for Janssen, Celgene, Takeda, Amgen, Merck Sharp and Dohme, Bristol-Myers Squibb and Novartis; PS has reported advisory boards, honoraria and research support from Amgen, Celgene, Janssen, Tanken, Karyopharm; MVM has reported honoraria from Janssen, Celgene, Amgen, Takeda; EZ has reported honoraria and advisory boards for Amgen, Bristol-Myers Squibb, Janssen and Celgene; RH has reported consultant and advisory

Table 7. Summary of recommendations

The diagnosis of MM must include the criteria updated in 2014 by the International Myeloma Working Group.
Immediate treatment is not recommended for patients with indolent myeloma.
For patients < 70 years in good clinical condition, induction followed by high-dose therapy with ASCT is the standard treatment.
For relapsed/refractory MM, the most commonly used regimens are proteasome inhibitor- or lenalidomide-containing regimens. New triplet combinations are increasing PFS.
In advanced cases, pomalidomide plus low-dose dexamethasone and daratumumab are approved.

ASCT, autologous stem cell transplantation; PFS, progression-free survival; MM, multiple myeloma.

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Table 8. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs,. . .), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [49].

boards from Amgen, Takeda, Bristol-Myers Squibb and Celgene, honoraria for Amgen, Bristol-Myers Squibb, Takeda, Celgene and Janssen and research funding from Takeda, Novartis, Amgen and Janssen; MAD has reported honoraria from Janssen, Celgene, Amgen and Takeda; HL has reported advisory boards and honoraria from Amgen, Celgene, Bristol-Myers Squibb, being a member of the speaker's bureau of Janssen-Cilag, Amgen, Celgene, Bristol-Myers Squibb and research support from Takeda and Amgen; HE has reported advisory boards, honoraria and research support from Janssen and Celgene and being a member of their speaker's bureau, advisory boards and honoraria from Amgen and Novartis and being a member of their speaker's bureau; SZ has reported research support from Takeda, Celgene, Janssen, advisory boards for Takeda, Celgene, Janssen and Novartis; TF has reported advisory boards for Celgene, Janssen, Takeda and Amgen and being a member of the speaker's bureau of Celgene, Janssen, Takeda and Amgen; ET has reported honoraria from Amgen, Bristol-Myers Squibb, Celgene, Janssen, Novartis, Takeda, research support by Amgen, Celgene and Janssen and participation in the steering committee of Amgen and Takeda and in the data monitoring committee of Celgene; HG has reported research support and honoraria from Celgene, Janssen, Chugai, Novartis and Bristol-Myers Squibb and advisory boards for Janssen, Celgene, Novartis, Amgen Takeda and Bristol-Myers Squibb; CB has reported research funds from Roche and Janssen and being a member of the speaker's bureau of Roche, Janssen and Pfizer; HAL, MC and MA have declared no conflicts of interest.

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